PSJ2 Exh 83

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OxyContin Meeting
April 23, 2001

The meeting was held on April 23, 2001 from 2:00 PM until 4:00 PM in the Potomac Room of the Parklawn Building. The following people were in attendance:

Representatives from PPLP
Michael Friedman – Exec VP and Chief Operating Officer
Mary Garfield – Coordinator II, International R&D
Joe Gimigliano – Systems Architect
Paul Goldenheim, MD – Executive VP, Worldwide R&D
J. David Haddox, MD, DDS – Sr. Medical Director, Health Policy
Lynn Kramer, MD – Vice President Medical Research
Chris Prue, RPh - Director Regulatory Affairs
Robert Reder, MD - VP Medical Affairs and Worldwide Drug Safety
Tony Santopolo, MD - VP Regulatory Affairs
Howard Udell, JD – Exec. VP, General Counsel

Representatives from FDA Division of Drug Marketing, Advertising and Communications:
Thomas Abrams, RPh – Director
Mark Askine, RPh – Branch Chief, Enforcement and Review Branch III
Spencer Salis, PharmD – Review Officer

Representatives from FDA Division of Anesthetic, Critical Care & Addiction Drug Products:
John Jenkins, MD – Director, ODE II
Cynthia McCormick, MD - Director
Bob Rappaport, MD - Deputy Director
Thomas Papoian, PhD - Supervisory Pharmacologist
Sharon Hertz, MD - Medical Officer
Gerald Dalpan, MD – Medical Officer
Lisa Basham, MS – Regulatory Project Manager
Kim Compton, RPh – Regulatory Project Manager
Suliman AlFayoumi, PhD – Biopharmaceutics Reviewer
Michael Theodorakis, PhD – Acting Chemistry Team Leader

Representatives from Controlled Substances Staff
Deborah Leiderman, MD - Director
Sylvia Calderon, PhD – Interdisciplinary Scientist
Corinne Moody - Science Policy Analyst

Other FDA Representatives
Steve Koepke, PhD – Division Director, DNDC2-ONDC
Mary Ortuzar – Policy Analyst, EOS
Mary Dempsey – Project Manager, OPDRA, DDRE II
Martin Pollock, PharmD – Safety Evaluator, OPDRA, DDRE II

Lynn Whipkey – General Attorney, OCC
Laura Bradbard – Press Office

The meeting began with Dr. McCormick giving introductory comments and indicating that, while PPLP had requested the meeting, the Agency was there to gain a better understanding of where the problems lie and to provide comments and suggestions on a Risk Management program for OxyContin. The results of this program should not be measured on quality and appearance but effectiveness. Results are needed; results that we can measure. These results will be used as feedback for making additional improvements to the program. The Agency is looking at all opiates but immediate attention is being given to ours – "it is the bad actor". There will be grave concern if this problem continues. The Agency is looking for specific proposals from PPLP.

Dr. Goldenheim (PPLP) provided the sponsors introductory comments and indicated that we shared the Agencies concerns and that we were taking this problem very seriously, which is why we had asked for this meeting. He described our concern regarding the misuse and abuse of our product and our desire to ensure that the product remains accessible for appropriate pain patients. He indicated that we had suggestions in several areas for their consideration. The proposals included suggestions; (1) in marketing for good promotional practices, (2) for labeling changes, (3) distribution changes, including a decision that PPLP has made to temporarily suspend distribution of the 160 mg tablet in the United States, (4) product development, where we planned to update the Agency on our development activities and finally (5) surveillance, where we had a number of initiatives planned as well as some that have started.

Dr. Pollock then presented a summary of information that had been derived from IMS and NDTI involving OxyContin. It was noted, from 1995 to present there had been a shift in prescribing patterns out of oncology specialties into family practitioners and, when looking by indication, mentions of neoplasm were decreasing and musculoskeletal disease were increasing. Musculoskeletal disease included such terms as lumbago, myalgia and other back pain related terms. Dr. Pollock compared the number of mentions in IMS of OxyContin to MS Contin and noticed that while MS Contin prescribing had remained relatively constant, OxyContin had increased 10 fold. The Agency implied that this was a trend they were concerned with. Mr. Friedman noted that these observations were consistent with our understanding of the data we have seen.

Dr. Hertz then summarized her thoughts on the OxyContin package insert. She would like the knowledge gained from the experience with the product on the market added to the abuse and adverse event section of the insert. She would like to see improvements throughout the drug abuse section. With regard to the indication, she thinks it is quite broad and may not be adequately expressing a proper description to identify the appropriate patient profile for this product. OxyContin is not necessarily the first opioid to be used and it should not be an intermittent opioid. We should take out some of the information in the clinical trials section that is not strong, such as the descriptions of the open label studies and the active comparator trials. We should consider a black box warning for overdose, abuse and death.

She would also like to see educational efforts increased possibly including a Medguide for patients on the risks of overdose and the abuse of opioids as well as risks for use by others than those for whom it was prescribed. She believes that there is a perception that oxycodone is safer than morphine. She thought that there could be improved education on diversion risk for prescribers. PPLP said that we had educational materials on diversion risk for both practitioners and pharmacists. FDA indicated that the materials did not mention OxyContin and failed to educate on the risks of OxyContin diversion. It was pointed out that this was deliberately void of mentions of OxyContin so as not to be perceived that this was just a disguised promotion for our product. PPLP believed that this effort was appropriate for all prescription drugs that can be abused, not just our product.

The Agency mentioned a Federal Register Notice about an upcoming meeting of the Anesthetic and Life Support Drugs Advisory Committee, June 14 and 15. This meeting will include a discussion of opioid use and abuse and the Agency may use OxyContin as an example or case study. [Post meeting note – The Federal Register Notice will not issue until May and at the current time the Agenda just refers to opiates in general.]

Dr. McCormick supported Dr. Hertz's views on the labeling. She said that many studies in the clinical trials section of the labeling grew out of a "pain model mentality" in the early nineties. The patients were enrolled in an "artificial setting" and these trials are the data that supports our current advertising and promotional efforts. She indicated that these patients were only on, for example, nonsteroidals and OxyContin became the next logical step. She indicated that it was time to "set the record straight" and look at some of these trials that should have never gone into the label for OxyContin. Our indication is too broad and this product shouldn't be used for conditions such as lumbago. Ambulatory and post-operative use are not appropriate for this product. She believes that the perception of OxyContin is that "it is good for whatever ails you" and that needs to be changed. Dr. Haddox noted that the diagnosis alone does not indicate anything about the appropriateness of the use of OxyContin. He said that diagnosis codes do not capture "intensity" of pain experienced by the patient.

Dr. Jenkins added that the labeling change needed is not just a couple words, large sections will need to be revised.

Dr. McCormick summarized this discussion by saying "major overhaul is my message". The prescribing of OxyContin is creeping into a whole population of people where it doesn't belong. Just rewriting the abuse and dependence section won't help much, that part of the insert is not a pivot point. She said that all opioid analgesics would be subjected to the same standards.

Howard Udell noted that PPLP would be willing to make the proposed changes at the time the FDA requests other Schedule II and III sponsors make these same changes. Michael Friedman indicated the PPLP would look at the changes proposed to the indication and consider making the changes.

Dr. McCormick responded that a number of the changes being proposed were specific to OxyContin. She added that the Agency would get to our competitors but the discussion today was about the problem of OxyContin.

Dr. Hertz added that she believed that doctors did not have the right perception about the use of OxyContin. The implication was that the prescribing behavior is too casual, "this is not a big deal". She then stated that there is a real difference (in sales growth) between OxyContin and MS Contin – Why?

Michael Friedman offered that, at the time OxyContin was launched, PPLP ceased any significant promotional efforts with MS Contin. Also, in the last five years, there has been a more aggressive approach to pain management in medical practice and that these trends FDA is noticing are in line with the way the practice of pain management has evolved.

Tom Abrams interjected that we need to correct a misconception that this product is different than morphine. This has to be an extensive educational effort to consumers and health care practitioners. He would also like to see nationwide market research from health care practitioners to determine what the message is the doctors are getting from our promotional efforts.

Michael Friedman then described our efforts in trying to anticipate problem areas for OxyContin and briefly mentioned the model which identified 100 counties where our efforts are going to be focused. Dr. McCormick then stated that this was an action item, she would like to see a proposal from PPLP for active surveillance of the abuse and diversion problem and which measures specific outcomes. She wants something in place to trigger a next step if our surveillance isn't effective. Mr. Abrams then reiterated his suggestion for a nationwide educational campaign and that we need to refocus our promotional materials and make the risks of abuse and diversion more prominent.

On the issue of packaging and distribution, FDA suggested possibilities to consider including unit of use packaging, increased warnings for patients and families, central distribution, and restrictive prescribing. It was asked what the package size was for OxyContin. Michael Friedman replied that our largest bottle was a 100 count and this seemed to eliminate any further discussion of unit of use packaging. Howard Udell said that we liked the idea of increased warnings for patients and families and asked for suggestions as to how we would do this.

The discussion then turned to our product development efforts. Dr. AlFayoumi, from the Division of Biopharmaceutics, then presented one overhead with summary thoughts from a biopharmaceutics perspective.

The current formulation is compositionally proportional for the 10, 20, 40, and 80 mg strengths. Therefore reformulation to include an antagonist would require a bioequivalency trial for the highest strength (80 mg) and for the 160 mg since it is not the

same formulation. In Vitro dissolution (meeting F_2 Criteria) comparisons would be required for the 10, 20 and 40 mg strengths. In the bioequivalence studies, we would be required to measure naloxone levels as well oxycodone levels. Depending upon the magnitude of the compositional change to incorporate the antagonist, a food effect study may also be needed. Literature support alone for the reformulation is not sufficient.

In addition there was discussion of a bioavailability study with crushed tablets and that pharmacokinetic data alone may not be sufficient to measure withdrawal effects for intranasal use. PPLP will need to be creative in order to assess the abuse liability and we may need to include a subset of "addicts" in order to assess the abuse deterrence of the reformulation.

Dr. Goldenheim then provided an overview of our development efforts with both naloxone and naltrexone combinations and noted that we had been working in this area for several years. He indicated that our initial work was with naltrexone because we had been told by FDA, DEA, and NIDA that the abuse of prescription opioids was principally oral. In the last few months we have learned that OxyContin is being abused intranasally and intravenously. As a result, we began efforts with naloxone. Our goal is a bioequivalent product to OxyContin. We have learned that there may be stability issues with the naloxone. He emphasized our desire to partner closely with FDA to ensure rapid development of this product. He also noted that the initial work was being done on the 10, 20, and 40 mg strengths because combining antagonists with higher doses of opioids may be a problem for some patients who are more tolerant and physically dependent.

Dr. McCormick indicated that the Agency can help in pointing out potential pitfalls of an oxycodone/naloxone combination but may not be able to suggest any fixes. PPLP was encouraged to submit a data package and meeting request for a meeting to discuss a reformulation. Dr. Jenkins asked if we could develop a formulation that isn't so easily crushed. Dr. Goldenheim said that we can formulate such a product but then it will be very difficult to have oxycodone release from the formulation properly for the patient.

On the issue of prospective monitoring and surveillance with feedback, it was suggested that PPLP follow the model that has been developed for Actiq. It was suggested that PPLP download the paper copy of the program as provided to the sponsor for Actiq from FDA's website. [Post Meeting Note: It has been determined that this document is not available on FDA's website and the availability of this document is under discussion at present.]

A discussion of collaborative efforts followed. It was agreed that the Office of Public Affairs (FDA's Press Office) does talk to the Press Office at corporate sponsors. The PPLP spokesperson should be in contact with Laura Bradbard at FDA regarding any collaboration on media issues. It was asked if FDA could help in obtaining autopsy reports from Virginia. Dr. Jenkins replied that FDA could not get them any easier than PPLP can. Dr. Rappaport added that "as soon as you bring us a product that is an abuse deterrent, we will turn that around as quickly as possible".

Further discussion ensued with regard to a level playing field. Dr. McCormick reiterated that "we are very aware of that but we have a problem here and now with OxyContin". In due time other manufacturers will be contacted but the first problem is this product.

FDA is interested in receiving our proposed labeling changes regarding abuse and diversion and indicated that we should submit these proposals under the current labeling application which is in house (pending at FDA). We will send our changes to FDA in a word file and they will respond with all of the labeling recommendations to us within two weeks. In addition they expect to receive a proposal for active surveillance from us in two weeks to a month. [Post Meeting Note: Due to difficulties in obtaining a copy of the Actiq surveillance program, this action item has no firm target date yet.] The marketing data that FDA requested in the April 20, 2001 teleconference is expected within two weeks as well.

Dr. Jenkins concluded the meeting by stating that OxyContin is a useful product when used by the right patients. Some of the efforts discussed today may result in a reduced market share or reduced sales. However product withdrawal is a potential risk management tool available to FDA if they can't get this problem under control. FDA has learned from this situation that the information put in the label back at the time of product approval did not adequately address the risks associated with this product and this needs to be corrected.